REVIEW

Commentary on Cochrane review of neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

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Abstract

In recent years there has been much debate and controversy surrounding the efficacy and safety of neuraminidase inhibitors for influenza, in part because the data underlying certain efficacy claims were not available for independent scrutiny. In 2014, a Cochrane review was published, based exclusively on an almost complete set of clinical study reports and other regulatory documents. Clinical study reports can run to thousands of pages, providing an extensive amount of information on the planning, conduct and results of each trial. After a protracted campaign to obtain the reports, the manufacturers of the medications provided them unconditionally. The review authors subsequently published the underlying documents simultaneously with the Cochrane review, endorsing the concept of open science. In the following commentary, the background to and results of this review are summarized and put into clinical context.

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The Cochrane review – 2006 to 2009: published evidence only

The publically available evidence base for neuraminidase inhibitors has changed dramatically over the past 8 years. This change has not come about through the results of new trials being published in peer-reviewed journals. Rather, information that was previously treated as confidential, such as evidence available only to regulators, became publically available. The change was set in motion by a Japanese paediatrician who, during the H1N1 outbreak of 2009, commented on the Cochrane review of neuraminidase inhibitors for adults published in 2006 [1]. Dr Keiji Hayashi questioned Cochrane's finding that oseltamivir reduces the risk of complications of influenza, pointing out that this conclusion was based on a manufacturer-authored, pooled analysis of manufacturer-sponsored randomized controlled trials, eight of which were unpublished [2] (to this day the eight trials remain unpublished). To address readers' comments, authors of Cochrane reviews are required to respond within 6 months, hence the neuraminidase inhibitors review authors set about obtaining the unpublished data. Initially, they were unsuccessful [3] and the data from the unpublished trials were not included in the updated 2009 version of the review [4].

The Cochrane review – 2009 to 2012: partial clinical study reports

In late 2009, the manufacturer of oseltamivir released part of the clinical study reports (CSRs) for all ten trials. CSRs are extensive documents reporting on clinical trials used to obtain regulatory approval [5]. Roche (Basel, Switzerland) did this in response to the 2009 Cochrane review of adults documenting that the majority of oseltamivir data had never been published and media reporting indicating that at least one major published

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trial was ghost-written [7]. The partial CSRs that Roche provided were still insufficient to properly address Hayashi's comment. Further requests to the manufacturer were initially not fruitful and the Cochrane researchers turned to the European Medicines Agency (EMA), which introduced a policy of sharing CSRs with third parties in late 2010. During the process of obtaining oseltamivir CSRs from EMA, work on the 2012 version of the Cochrane review, which now included adults as well as children [6], was finalized, hence that review was only based on a subset of the relevant information (15 oseltamivir and ten zanamivir studies). In addition, the EMA had in its possession a full CSR for only one oseltamivir study. (EMA had no data on zanamivir.)

The Cochrane review – 2012 to 2014: full clinical study reports

In 2013, after a 4-year public campaign led by the *BMJ* (bmj.com/tamiflu), Roche unconditionally released full CSRs for all 77 sponsored clinical trials to the Cochrane group. The manufacturer of zanamivir (GlaxoSmithKlein; Brentford, UK) also provided a complete set of requested CSRs hence the 2014 version of the review [8] is based on the majority of relevant information although Japanese and Chinese studies of oseltamivir (three trials in total) are not included because of lack of complete CSRs.

The 2014 analysis included 46 randomized, placebo-controlled trials (20 of oseltamivir and 26 of zanamivir) on adults and children with confirmed or suspected exposure to naturally occurring influenza. Despite the title of the review including the words 'healthy adults', the elderly and patients with chronic diseases were included. The only population excluded comprised immunocompromised patients. All treatment trials recruited patients with influenza-like illness, defined as fever plus one constitutional symptom and one respiratory symptom. Influenza status was determined post-randomization using results from culture test and serology. Efficacy analyses in the Cochrane review were conducted on the intention-to-treat population of all randomized patients with influenza-like-illness, mimicking the situation of most clinicians in general practice, and safety analysis was based on all patients receiving at least one dose of study medication.

Results showed both oseltamivir and zanamivir have similar effects in terms of efficacy. Both medications reduce the time to first alleviation of symptoms of influenza-like illness in adults by around 10%. The reduction for oseltamivir was 0.70 days (95% CI −1.05 to −0.35 days, p <0.0001) whereas for zanamivir it was 0.60 days (95% CI −0.81 to −0.39 days, p <0.00001). There was no indication that the oseltamivir effect differed in subgroups of patients such as the elderly or those with chronic obstructive airways disease. However, because trials on these subgroups of patients were under enrolled, the manufacturer chose to combine the three trials in the elderly in a single clinical study report. The same occurred for the two trials in patients with chronic obstructive airways disease (Fig. 1). There was no evidence of a difference in treatment effect for zanamivir in the influenza-infected and non-influenza-infected subgroups (p = 0.53), suggesting that the effect of the neuraminidase inhibitors is not specific to influenza (Fig. 2). (Data were not available in a usable format to test this for oseltamivir.)

In children, the evidence is based on a small number of trials. For oseltamivir, time to first alleviation of symptoms was reduced in one trial of otherwise healthy children by 1.2 days (95% CI −1.9 to −0.49 days, p = 0.001) but not in three trials of children with asthma where patients in the oseltamivir groups took 0.2 days longer for initial alleviation of symptoms (95% CI −0.46 to 0.89 days, p = 0.53). There were only two trials of zanamivir in children with insufficient evidence of treatment

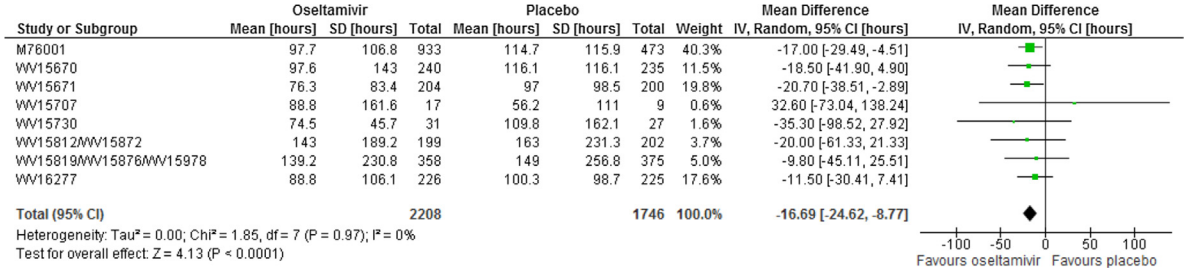

FIG. 1. Time (in hours) to first alleviation of symptoms in oseltamivir treatment trials of adults. (Please note that Study WV15812/WV15872 includes two under-recruited trials of patients with chronic obstructive airways disease that were combined by the manufacturer before reporting in the clinical study report and similarly Study WV15819/WV15876/WV15978 includes three under-recruited trials of the elderly that were combined by the manufacturer before reporting in the clinical study report. All other studies were in otherwise healthy adults.)

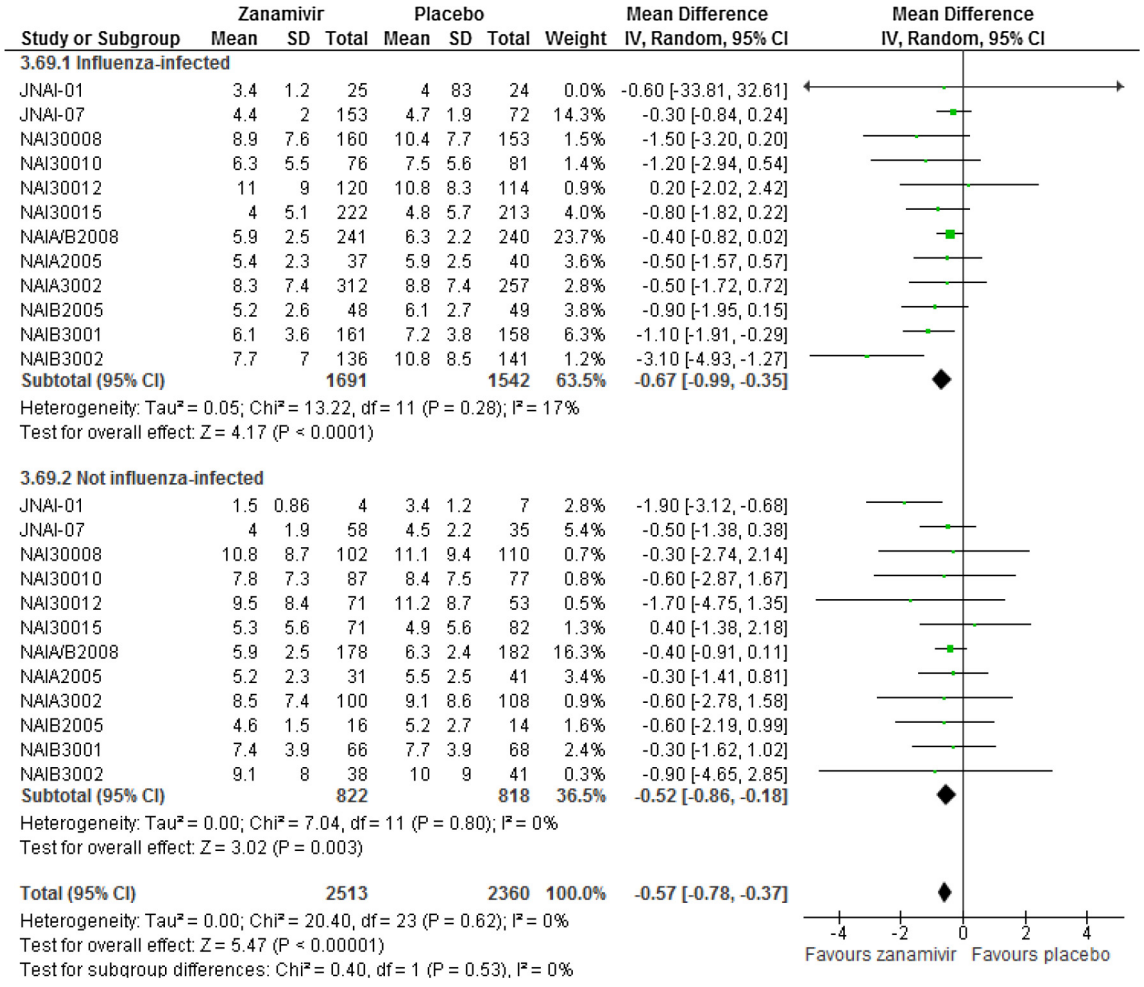

FIG. 2. Time (in days) to first alleviation of symptoms in zanamivir treatment trials of adults by infection status.

effect but suggesting a reduction of 1.08 days (95% CI −2.3 to 0.15 days, p = 0.08).

In terms of prevention of serious adverse outcomes there was no evidence that oseltamivir reduced the risk of hospitalization (risk difference (RD) 0.15%, 95% CI −0.78 to 0.91) or complications classified as serious or leading to study withdrawal (RD 0.07%, 95% CI −0.78 to 0.44). There were inconsistent results for the outcome classified as 'pneumonia' across the different drugs, age groups, and whether medication was given for treatment or prophylaxis. Meta-regression showed that the inconsistency was probably due to how the outcome was assessed and recorded in the trials. In trials where pneumonia was reported as an adverse event there was evidence of a treatment effect (relative risk (RR) 0.54, 95% CI 0.37–0.78) but in trials where a more detailed diagnostic form including X-ray confirmation was used, there was no evidence of a treatment effect (RR 1.0, 95% CI 0.70–1.45).

In prophylaxis trials, oseltamivir and zanamivir also showed similar modest effects for efficacy. They reduced the risk of symptomatic influenza in individuals (oseltamivir: RD 3.05%, 95% CI 1.83–3.88; zanamivir: RD 1.98%, 95% CI 0.98–2.54) and in households (oseltamivir: RD 13.6%, 95% CI 9.52–15.47; zanamivir: RD 14.84%, 95% CI 12.18–16.55) but there was no evidence of an effect on asymptomatic influenza (oseltamivir: RR 1.14, 95% CI 0.39–3.33; zanamivir: RR 0.97, 95% CI 0.76–1.24). Other prophylaxis efficacy outcomes of the review could not be assessed as planned. Influenza-like illness (not diagnosed as influenza) was not defined in the CSRs or fully reported and prophylaxis trials were not designed to test the effect of drug on interruption of person-to-person viral spread. In exploratory analysis of the four prophylaxis trials of individuals using a definition for influenza-like illness of two or more symptoms out of nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever there was no evidence that oseltamivir reduced risk of illness (RR 0.95, 95% CI 0.86–1.06). However, oseltamivir reduced the risk of fever (RR 0.62, 95% CI 0.42–0.93) and reduced the probability of testing positive for influenza (RR 0.59, 95% CI 0.41–0.85).

These results suggest that oseltamivir suppresses fever and viral shedding but does not reduce the risk of symptomatic illness.

Although outcomes were similar for efficacy, they were not in terms of harms. Nausea, vomiting, headache, psychiatric syndromes, renal events and reduced antibody response to influenza infection were all associated with oseltamivir in various subgroups of trials whereas there was no evidence suggesting that zanamivir is associated with an increased risk of adverse events. However, a limitation of the zanamivir trials is that the placebo contained lactose powder, which may have masked a potential adverse effect of bronchospasm.

The clinical implications of these results are debatable. There is insufficient evidence that neuraminidase inhibitors reduce the risk of rare but serious consequences of influenza such as pneumonia and hospitalization. However, they appear to reduce symptoms of influenza-like illness. The symptomatic relief is not specific to influenza, is modest, and may be similar to that of other cheaper over-the-counter medications such as paracetamol, although this has never been assessed, despite calls for this to happen during the recent influenza 'pandemic' [9]. Furthermore the more commonly prescribed oseltamivir is associated with relatively common side effects (numbers needed to harm around 20 to 30) such as nausea, vomiting and headache. More worryingly, prophylaxis studies indicated that oseltamivir is also associated with rarer but more serious harms including psychiatric syndromes and renal adverse events – and the reduction in antibody response could have implications for future risk of infection.

The Cochrane review by Jefferson *et al.* [8] is novel in that it is the first to be based solely on an almost complete set of clinical study reports (which were made publicly available on the day of its publication) and other regulatory information. Therefore reporting bias, a common limitation of systematic reviews, has been greatly reduced. Furthermore, the review has been conducted independently from the manufacturers of the medications. A recent publication has shown that this distinction may be important [10]. However, a limitation is that all included trials are industry sponsored, trials of which significantly overestimate results when compared with non-industry trials [11,12], and another is that none were conducted in patients with severe influenza.

The complete set of clinical study reports can be downloaded from http://dx.doi.org/10.5061/dryad.77471

Transparency declaration

All authors have applied for and received competitive research grants. TJ, PD, CDM, MJ and CH were co-recipients of the NIHR grant to carry out the 2014 Cochrane review (http://www.nets.nihr.ac.uk/projects/hta/108001). In addition the following apply. Dr Jefferson receives royalties from his books published by Blackwell and Il Pensiero Scientifico Editore, Rome. He is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011–13 Dr Jefferson acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu [Roche] and in a labour case on influenza vaccines in healthcare workers in Canada. In 1997–99 Dr Jefferson acted as consultant for Roche, in 2001–02 for GSK and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral which did not get approval from the US Food and Drug Administration). In 2013 Dr Jefferson was a consultant for IMS Health and in 2014 he was on a retainer for a case of litigation on oseltamivir and zanamivir. Dr Doshi received €1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Prof. Del Mar was a Board member of two companies to commercialize research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010, receives fees for editorial and guideline developmental work and royalties from books, and is in receipt of institutional grants from NHMRC (Aus) (587801, 1044904), NIHR (UK) and HTA (UK) (10/80/01) and from a private donor (for support of the editorial base of the Cochrane ARI Group). Prof. Heneghan receives payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (Evidence Based Toolkit series by Blackwell BMJ Books). Dr Onakpoya and Dr Jones have no additional interests to disclose.

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